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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/214,009	05/07/1999	NICO JOHANNES C M BEEKMAN	3898US	6111

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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	PAPER NUMBER
1645	22

DATE MAILED: 06/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/214,009	Johannes et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 25, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-6, 9-15, and 19-23* ~~is~~/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-6, 9-15, and 19-23* ~~is~~/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 02/25/02 (paper no. 20) in response to the non-final Office Action mailed 10/23/01 (paper no. 17). With this, Applicants have submitted a substitute specification.

Status of Claims

2) Claims 7, 8, 11 and 16-18 have been canceled via the amendment filed 02/25/02.

Claims 1, 2, 3-6, 9, 10, 12, 13-15, 19-21 and 23 have been amended via the amendment filed 02/25/02.

Claims 1-6, 9, 10, 12-15 and 19-23 are pending.

Claims 1-6, 9, 10, 12-15 and 19-23 are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

5) The objection to claims 1, 6, 12, 15, 18, 19, 21 and 23 made in paragraph 17 of the Office Action mailed 10/23/01 (paper no. 17) is withdrawn in light of Applicants' amendments to the claims.

6) The objection to the drawings made in paragraph 6 of the Office Action mailed 10/23/01 (paper no. 17) was in error and is withdrawn.

7) The objection to the specification made in paragraph 6 of the Office Action mailed 10/23/01 (paper no. 17) is withdrawn in light of Applicants' amendments to the specification.

Rejection(s) Moot

8) The rejection of claims 16-17 made in paragraph 16 of the Office Action mailed 10/23/01

(paper no. 17) under 35 U.S.C § 103(a) as being unpatentable over Meleon *et al.* (US 6,284,733) in view of Wiedemann *et al.* (*J. Pathol.* 164: 265-271, 1991), was in error and is moot in light of Applicants' previous cancellation of the claims.

Rejection(s) Withdrawn

9) The rejection of claims 1-6, 9, 10 and 12 made in paragraph 11 of the Office Action mailed 10/23/01 (paper no. 17) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claims and/or the base claim(s).

10) The rejection of claims 1-4, 12, 13, 19, 22 and 23 made in paragraph 13 of the Office Action mailed 10/23/01 (paper no. 17) under 35 U.S.C § 102(b) as being anticipated by Yatvin *et al.* (US 5,256,641 - Applicants' IDS), is withdrawn in light of Applicants' amendment to the claims and/or the base claim(s).

11) The rejection of claims 1, 5, 13, 14, 19 and 20 made in paragraph 15 of the Office Action mailed 10/23/01 (paper no. 17) under 35 U.S.C § 103(a) as being unpatentable over Yatvin *et al.* (US 5,256,641 - Applicants' IDS) or Haynes *et al.* (US 5,013,548) in view of Wiedemann *et al.* (*J. Pathol.* 164: 265-271, 1991), is withdrawn in light of Applicants' amendment to the claims and/or the base claim(s).

12) The rejection of claims 13-15 made in paragraph 16 of the Office Action mailed 10/23/01 (paper no. 17) under 35 U.S.C § 103(a) as being unpatentable over Meloen *et al.* (US 6,284,733) in view of Wiedemann *et al.* (*J. Pathol.* 164: 265-271, 1991), is withdrawn.

Rejection(s) Maintained

13) The rejection of claims 1, 5, 19 and 20 made in paragraph 15 of the Office Action mailed 10/23/01 (paper no. 17) under 35 U.S.C § 103(a) as being unpatentable over Haynes *et al.* (US 5,013,548) in view of Wiedemann *et al.* (*J. Pathol.* 164: 265-271, 1991), is maintained for reasons set forth therein and herebelow.

Applicants contend that Haynes discloses conjugating the peptide to the carrier molecule through a heterofunctional coupling agent. Applicants acknowledge that Haynes used MBS as the preferred coupling agent. Applicants assert that in an alternate embodiment, Haynes discloses coupling the peptide and carrier molecule through a spacer. Applicants state that such

is not the present invention as the claims recite a direct link between a peptide or antigen and a lipid or other carrier compound. With regard to Wiedermann *et al.*, Applicants argue that the P_3CS constructs disclosed in Wiedermann *et al.* are complex molecules consisting of three "palmitic acids" bound via ester or amide bonds to cysteine, and that these complex molecules are quite different from the simple palmitic acid taught in the present application. Applicants assert that the antigen or peptide and carrier compound are coupled in a "reversible and labile way".

Applicants' arguments have been carefully considered, but are non-persuasive. In Haynes' conjugate vaccine or immunogenic preparation, the peptide antigen is coupled to suitable carrier molecules "directly" (see column 2, lines 44-49). Haynes *et al.* teach that the peptides can also be conjugated to "other carrier molecules more immunogenic than tetanus toxoid" (see column 4, lines 65-68). The linkage of a carrier molecule to a peptide can be "direct". The conjugate vaccine comprises di-sulfide bonds (see first full paragraph in column 5; column 6, lines 46-49; first full paragraph in column 7; and columns 3 and 4). Haynes *et al.* used the same reagent, MBS ester, used by Applicants to produce their conjugate (see Example 1 of Haynes). Therefore, Haynes *et al.* is properly applied as the primary reference in the rejection made under 35 U.S.C § 103.

With regard to the Applicants' remarks on Wiedermann *et al.*, it should be noted that the recitation "palmitic acid" in the instant claim(s) encompasses all forms of palmitic acid, i.e., a complex and a non-complex molecule, i.e., a palmitic acid complex is not excluded from the scope of the claim(s). That the peptide or the antigen and the carrier compound are coupled in a labile way is implicit from the teachings of the prior art since it is well known in the art that disulfide bonds represent labile bonds. Instant claims, as drafted currently, do not recite that the coupling is "reversible". The feature upon which Applicants rely is not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993)*. For these reasons, the rejection stands.

14) The rejection of claims 1-6, 9, 10, 12 and 19-23 made in paragraph 16 of the Office Action mailed 10/23/01 (paper no. 17) under 35 U.S.C § 103(a) as being unpatentable over

Meloen *et al.* (US 6,284,733) in view of Wiedemann *et al.* (*J. Pathol.* 164: 265-271, 1991), is maintained for reasons set forth therein and herebelow.

Applicants contend that Meloen lacks disclosure of labile "binding" under physiological conditions and therefore, the proposed combination of Meloen and Wiedemann cannot render the present invention obvious.

The Applicants' argument has been carefully considered, but is non-persuasive. The relevance of labile "binding" in the instant invention is not understood. As clearly set forth in paragraph 16 of the Office Action mailed 10/23/01, Meloen *et al.* ('733) teach a LHRH or GnRH peptide of SEQ ID NO: 1 linked to a carrier compound via a disulfide bridge (i.e., bond) and a vaccine comprising the same. The disulfide bond represents a labile bond. Therefore, Meloen *et al.* ('733) qualifies as prior art under 35 U.S.C § 103. The rejection stands.

New Rejection(s)

Applicants are asked to note the following new rejection(s) made in this Office. The new rejections are necessitated by Applicants' amendments to narrow the scope of the claim(s) and/or the base claims.

Rejection(s) under 35 U.S.C § 102

15) Claims 1, 3, 5, 12 and 13 are rejected under 35 U.S.C § 102(e) as being anticipated by Golding (US 5,824,310).

The transitional phrases "comprising", "consisting essentially of" and "consisting of" define the scope of a claim with respect to what unrecited additional components or steps, if any, are excluded from the scope of the claim. The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986)*; *In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981)*; and *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts").

Golding discloses a vaccine comprising an antigenic component, such as, the V3 loop of the HIV-1 envelope (i.e., a peptide), a tumor antigen or the TNP hapten, conjugated to a

lipopolysaccharide of *Brucella abortus* via thioester linkage (see abstract; claims 1 and 4; column 3, lines 22 and 23; column 14, lines 43 and 44; and column 5, lines 15-20). The lipopolysaccharide component comprises the lipid A which is characterized by fatty acids (see column 1, lines 21-24). The vaccine may comprise multiple peptides (see column 5, lines 29-31). The vaccine comprises a pharmaceutically acceptable vehicle and/or adjuvant (see column 2, lines 17-20). That Golding's thioester linkage represents a labile bond that dissociates under physiologic conditions is inherent from the disclosure of Golding. The functions of lability and dissociation are considered as inherent properties inseparable from the prior art thioester linkage.

Claims 1, 3, 5, 12 and 13 are anticipated by Golding.

16) Claims 1-5, 12, 19, 20, 22 and 23 are rejected under 35 U.S.C § 102(b) as being anticipated by Jung *et al.* (EP 0,431,327 - original and the translated document).

The page numbers indicated below refer to the page numbers in the translated document.

Jung *et al.* disclose a synthetic conjugate vaccine of a microbial protein, a partial sequence (i.e., peptide) of such a protein or a tumor antigen and a lipoprotein or a lipopeptide (see pages 3 and 5; and claims). The conjugate comprises disulfide (-S-S-) (see page 4 and claim 3) and is suitable for immunization (see last two lines on page 6; and page 14 and 16). The lipopeptide or lipoprotein is N-palmitoylated (see paragraph bridging pages 5 and 6; the Figure on page 7). Example 1 teaches the synthesis of N-palmitoylated NP 147-158 peptide. The conjugation reaction involves disulfide formation (see page 9). The conjugate vaccine contained in PBS (i.e., a pharmaceutically acceptable compound) is used to immunize mice (see paragraph bridging pages 13 and 14). A method of producing the conjugate vaccine is taught (see pages 22-25). The functions of lability and dissociation are considered as inherent properties inseparable from the prior art disulfide linkage.

Claims 1-5, 12, 19, 20, 22 and 23 are anticipated by Jung *et al.*

17) Claims 1-5, 9, 10, 19, 20 and 22 are rejected under 35 U.S.C § 102(b) as being anticipated by Chang *et al.* (US 5,149,782).

Chang *et al.* disclose therapeutic conjugates comprising an antigen, such as, a protein, polypeptide, synthetic peptides, glycoprotein or nucleic acid, coupled to a palmitic acid or other fatty acids of varying length via a linkage that is cleavable (i.e., labile) under appropriate

conditions, for example, conditions extant at the target site (i.e., physiological conditions). The cleavable linkage is a disulfide linkage. See claims, claims 1, 2, 7, 10 and 11 in particular; column 2, lines 2-49; column 3, lines 9-13 and 17 and 18; column 3, lines 56 and 57; column 5, lines 9-23; and column 6, lines 31-45. Peptides that are synthetic are used (see column 3, lines 56 and 57). The linkage can be of irreversible or cleavable (i.e., reversible) types (see column 8, lines 2 and 3). A preferred cleavable linkage is a disulfide bond, which may be found between the SH group of Cys residues in a protein molecule. Active electrophilic S atoms can also be introduced by the use of SPDP. At the target tissue sites, the S-S bonds are cleaved. Cleavable bonds can also be constructed taking advantage of the slight acidic pH in target tissues (see third full paragraph in column 6). Two or more membrane blending agents (i.e., for example, peptide-peptide-fatty acid) can be interlinked in the conjugate (see column 2, lines 48 and 49). The membrane blending agent is coupled to a blocking agent via a cleavable linkage so that the blocking agent gets released (see column 2, lines 7-12 and 45-47). The blocking agent can be a monoclonal antibody, a ligand for a cell surface receptor or a short peptide (see column 2, lines 27-35 and 39-40). The blocking agent can also be a targeting agent such as, a **hormone** or growth factor which selectively directs the molecular conjugate to an appropriate target, (see column 6, lines first full paragraph). The composition is used *in vivo* for therapeutic and diagnostic purposes (see column 7, second full paragraph). A method of producing the conjugate composition of the invention is taught (see Examples).

Claims 1-5, 9, 10, 19, 20 and 22 are anticipated by Chang *et al.*

18) Claims 1, 3-5, 12, 19, 20, 22 and 23 are rejected under 35 U.S.C § 102(e) as being anticipated by Shen *et al.* (US 5,907,030, filed 1995).

Shen *et al.* disclose sulfhydryl-containing peptides or proteins comprising fatty acid-conjugated products with a disulfide linkage for delivery of the compounds to mammalian cells. The disulfide linkage in the conjugate is quite **labile** in the cells and thus facilitates intracellular release of the intact compounds from the fatty acid moieties (see abstract; and paragraph bridging columns 4 and 5). It is taught that fatty acids represent potentially the most useful carriers for the delivery of proteins and peptides (see column 4, lines 11-16). Sulfhydryl-containing compounds are peptides, proteins or oligonucleotides (see column 4, lines 59-65; and claims). The

sulfhydryl-containing biopolymer is attached to a fatty acid derivative via a **reversible** biodegradable disulfide bond so that the compound gets released into interstitial fluid as the result of disulfide bond reduction (see column 5, lines 31-38). The conjugate is administered to a mammal in an aqueous solution (see column 5, lines 61-63). The biopolymeric proteins and peptides are synthesized by solid-state synthesis (see column 7, lines 34-40). The conjugates are contained in pharmaceutically acceptable carrier or adjuvants (see first full paragraph in column 9). It is a particular advantage that the disulfide linkage between the fatty acid moiety and the peptide or protein may readily be reduced. The active peptide or protein molecules are released in intact form inside the target tissues or cells (see column 9, lines 44-48). Shen *et al.* disclose a method of producing a palmityl disulfide conjugate of BBI protein (see columns 11 and 13). The reduction of BBIssPal conjugate with DTT causes the detachment of the palmitic acid from the conjugate (see column 13, lines 49 and 50). BBIssPal was administered to mice (see Example 4). A palmitic acid conjugate of HRP, HRPssPal, is also taught in Example 9. That Shen's conjugate comprises a protein or peptide linked directly with palmitic acid is inherent from the disclosure of Shen *et al.*

Claims 1, 3-5, 12, 19, 20, 22 and 23 are anticipated by Shen *et al.*

19) Claims 1, 3, 5 and 12 are rejected under 35 U.S.C § 102(b) as being anticipated by Staufenbiel (*J. Biol. Chem.* 263: 13615-13622, 1988).

The term "vaccine" is viewed as the intended use of the product and is therefore not given any patentable weight.

Staufenbiel teaches a composition contained in a sodium phosphate solution comprising a protein (i.e., an antigen) linked to palmitic acid via labile and reversible thioester bonds. The deacylation (i.e., dissociation) of the compound appeared to be physiologically induced (see abstract; paragraph bridging 13619 and 13620; left column in page 13616; and left column on page 13621). It is taught that in most cases of proteins in eukaryotic cells, palmitic acid appears to be linked through thioester bonds to internal cysteines (see paragraph bridging left and right columns on page 13615).

Claims 1, 3, 5 and 12 are anticipated by Staufenbiel.

20) Claims 1, 3 and 5 are rejected under 35 U.S.C § 102(b) as being anticipated by Wan *et al.*

(*J. Cellular Physiol.* 145: 9-15, 1990).

Wan *et al.* teach a conjugate composition, HRP-SS-PDL, comprising horseradish peroxidase (HRP) linked directly to polylysine (PDL) via cleavable disulfide linkage, which was cleaved rapidly at the surface of a cell (see abstract and first paragraph under 'Results') and therefore, under physiological conditions. The conjugate contains reducible disulfide linkage and was purified by gel filtration (see page 10, left column). The conjugate was transported transcellularly during when the cleavage of disulfide linkage and the release of free HRP took place, i.e., under physiologic conditions (see page 10, right column; and page 13, right column).

Claims 1, 3 and 5 are anticipated by Wan *et al.*

Rejection(s) under 35 U.S.C § 103

21) Claims 13, 14, 19, 20 and 23 are rejected under 35 U.S.C § 103(a) as being unpatentable over Shen *et al.* (US 5,907,030, filed 1995) or Chang *et al.* (US 5,149,782) in view of Wong (*In: Chemistry of Protein Conjugation and Cross-linking.* CRC Press, Inc., London, Chapter 3, 49-73, 1993) and/or Staufenbiel (*J. Biol. Chem.* 263: 13615-13622, 1988).

The reference of Shen *et al.* is applied in this rejection because it qualifies as prior art under subsection (e) of 35 U.S.C § 102 and accordingly is not disqualified under U.S.C 103(a).

The teachings of Shen *et al.* or Chang *et al.* are explained above, which do not disclose the presence of a thioester bond between the peptide and the fatty acid in their composition and method.

However, the thioester bond or linkage is known in the art as an alternative labile or cleavable linkage. For instance, see pages 63 and 66 under section VI of Wong. The use of labile and reversible thioester bond(s) to produce an antigen-palmitic acid conjugate is well known in the art. For instance, see the teachings of Staufenbiel *supra.*

It would have been obvious to one of ordinary skill in the art at the time the invention was made to replace Shen's or Chang's disulfide linkage with Wong's or Staufenbiel's alternate, labile or cleavable linkage, such as, thioester linkage, to produce the composition and the method of the instant invention, with a reasonable expectation of success. Given that thioester bonds were already used in the art successfully in the production of cleavable antigen-palmitic acid conjugates as taught by Staufenbiel, substitution of one labile bond, such as, disulfide bond, with

another, alternate, art-known labile bond, such as, thioester bond would have been obvious to one of ordinary skill in the art, would have been well within the realm of routine experimentation and would have expected to bring about similar effects or results.

Claims 13, 14, 19, 20 and 23 are *prima facie* obvious over the prior art of record.

22) Claims 15 and 21 are rejected under 35 U.S.C § 103(a) as being unpatentable over Chang *et al.* (US 5,149,782) in view of Wong (*In: Chemistry of Protein Conjugation and Cross-linking.* CRC Press, Inc., London, Chapter 3, 49-73, 1993) and/or Staufenbiel (*J. Biol. Chem.* 263: 13615-13622, 1988, as applied to claim 13 or 19 above, and further in view of Meloen *et al.* (US 6,284,733, already of record).

The teachings of Chang *et al.* as modified by Wong and/or Staufenbiel are explained above, which do not disclose the peptide in their composition and method to be SEQ ID 1.

However, Meloen *et al.* ('733) teach the use of LHRH or GnRH peptide of the amino acid sequence, SEQ ID NO: 1, and its conjugation via a labile disulfide bond (see abstract; columns 6 and 9; and claims).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to replace Chang's peptide with Meloen's ('733) specific GnRH peptide of SEQ ID NO: 1 in Chang's composition as modified by Wong to produce the composition of the instant invention with a reasonable expectation of success, because Chang *et al.* expressly teach that a hormone can be used in their composition and method. One skilled in the art would have readily understood that Meloen's GnRH peptide of SEQ ID NO: 1 qualifies as a hormone. Substitution of a generic peptide with a specific, art-known hormone peptide in a conjugate containing labile bonds is well within the realm of routine experimentation and would yield a similarly effective product.

Claims 15 and 21 are *prima facie* obvious over the prior art of record.

23) Claims 1, 3, 4, 6, 9, 10, 19 and 21 are rejected under 35 U.S.C § 103(a) as being unpatentable over Chang *et al.* (US 5,149,782) in view of Russell-Jones *et al.* (WO 91/02799) or Meloen *et al.* (US 6,284,733, already of record) (Meloen *et al.*, '733).

The disclosure of Chang *et al.* is described above, which does teach that the composition may comprise a hormone, but does not teach the hormone to be a peptide of SEQ ID NO: 1.

However, Russell-Jones *et al.* disclose the concept and method of fusing or conjugating at least one or tandem repeats of LHRH (i.e., GnRH), Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly (i.e., SEQ ID NO: 1) to a lipid-containing carrier (see page 2; paragraph bridging pages 3 and 4; page 7; page 13; and page 29). Russell-Jones *et al.* teach the use of LHRH dimers (see Figure 4 and page 13) or multimers (see Figure 5; Table 1; pages 13 and 21; Examples 1 and 6; and claims 5-9 and 12-14). Russell-Jones *et al.* teach the advantage of using tandem repeats of LHRH (i.e., peptide sequences) over a single insert (see page 6, lines 26-29).

Meloen *et al.* ('733) teach the use of dimeric LHRH or GnRH peptide of the amino acid sequence, SEQ ID NO: 1, and its conjugation via a labile disulfide bond (see abstract; columns 6 and 9; and claims).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to replace Chang's peptide or polypeptide with Russel-Jones' GnRH tandem repeat or Meloen's dimeric GnRH peptide to produce the composition and the method of the instant invention, with a reasonable expectation of success, because Chang *et al.* teach that the conjugate can contain a hormone and that two or more agents can be interlinked in the conjugate. A skilled artisan would readily understand that Russel-Jones' or Meloen's GnRH qualifies as a hormone. Substitution of a generic peptide with a specific, art-known hormone peptide in a conjugate containing labile bonds is well within the realm of routine experimentation and would yield a similarly effective product.

Claims 1, 3, 4, 6, 9, 10, 19 and 21 are *prima facie* obvious over the prior art of record.

Prior Art

24) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicant's disclosure:

- Meloen *et al.* (*Vaccine* 12: 741-746,1994) (Meloen *et al.*, 1994) teach the concept and method of conjugating or fusing tandem repeats of the amino acid sequence of the GnRH peptide to a protein carrier for vaccination purposes (see abstract; and Materials and Methods').

Remarks

25) Claims 1-6, 9, 10, 12-15 and 19-23 stand rejected.

26) The Applicants' amendment necessitated the new ground(s) of rejection presented in this

Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

27) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

28) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

June, 2002

S. DEVI, PH.D.
PRIMARY EXAMINER